A new method of antitumor therapy with a high dose of TNF perfusion for unresectable liver tumors.

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There are primary and secondary malignant liver tumors for which principal treatment is surgical resection. There is no established treatment for unresectable malignant liver tumors, however, and the prognosis for these is quite poor. An effective treatment for malignant liver tumors is thus urgently needed. Recent advances in molecular biology have uncovered the structures and/or functions of many cytokines thought to have a strong relation with the mechanisms of the antitumor effect of biological therapies. Availability of those cytokines in large amounts and homogeneously owing to advances in recombinant technology makes it possible to use them clinically. Among cytokines demonstrating antitumor activities, tumor necrosis factor-alpha (TNF-alpha) is one of the strongest. However, severe toxicity such as hypotension, abnormalities in liver function, leukopenia, chill and thrombus formation makes TNF-alpha difficult to use systemically as an antitumor drug. To enhance cytotoxicity while decreasing the side effects, especially hypotension, we developed a mutein called TNF-SAM2 by protein-engineering. The biological activity of TNF-SAM2 was more beneficial than TNF-alpha for antitumor therapy, since its side effects were milder. In contrast, using the isolated limb perfusion (ILP) method against malignant melanoma and soft tissue sarcoma of the extremities in combination with TNF-alpha and melphalan, a high response rate of 70-100% was observed. These observations led to the re-evaluation of TNF as an antitumor drug. A preliminary clinical trial was done using TNF-alpha combined with the formation of a closed circuit (isolated hepatic perfusion method) targeting the liver and a response rate of over 75% was achieved against malignant liver tumors. To isolate the liver from the systemic circulation, however, required a laparotomy, so that patients were subjected to excessive surgical stress. Isolated hypoxic hepatic perfusion (IHHP) using balloon catheters is a treatment developed to overcome such stress and we are planning to do clinical trials of IHHP with TNF-SAM2 in combination with a chemotherapeutic agent against malignant liver tumor patients. IHHP combined with TNF-SAM2 and a chemotherapeutic agent might be more beneficial in antitumor effects as well as in maintaining good quality of life (QOL) for the patient.

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Pharmacokinetics and pharmacodynamics of a recombinant human granulocyte colony-stimulating factor.

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Granulocyte colony-stimulating factor (G-CSF), a hematopoietic growth factor, is a clinically effective drug used to promote neutrophil recovery in patients with chemo- or radiotherapy-induced neutropenia. We have reviewed the pharmacokinetic and pharmacodynamic properties of three kinds of G-CSFs: E. coli derived G-CSF, CHO-derived G-CSF, and mutein G-CSF. The clearances of G-CSFs are saturable and autoinducible in experimental animals and humans. That is, the systemic clearances of G-CSFs decrease as the dose injected increases and approaches a constant value. Both saturable and nonsaturable processes are involved in G-CSF elimination. Also, the systemic clearances of G-CSFs are increased by repeated administration of G-CSF. Although the relative bioavailability of G-CSFs after subcutaneous administration is approximately 60%, the increase in peripheral white blood cells or neutrophils is greater than that after intravenous administration at the same dose. The effects of G-CSFs seem to be time dependent rather than AUC dependent, considering that mean residence time of G-CSFs in the plasma is longer after subcutaneous administration than that after intravenous administration. There is a slight difference in the pharmacokinetics of E-coli- and CHO-G-CSF although they seem to be pharmacologically equivalent. The correlation between G-CSF clearance and peripheral neutrophil counts in the patients suggests that G-CSF receptors contribute to G-CSF clearance. Quantitative pharmacokinetic analysis using mutein G-CSF shows that the G-CSF receptor plays a major role in saturable G-CSF clearance, and that this saturable process accounts for approximately 80% of the total clearance at low doses. That is, the degradation following the receptor-mediated endocytosis in bone marrow might be a major clearance system of G-CSF at a physiological blood level. The G-CSF receptor in bone marrow might work not only as a signal transducer for differentiation and proliferation of granulopoietic precurcer cells but as a regulator of G-CSF levels in blood. In addition, at high doses, glomerular filtration in the kidneys is the major process for nonsaturable G-CSF clearance. At present, polyethylene glycol derivatives of G-CSF are being developed to reduce the frequency of G-CSF administration.

Local immunotherapy with rhTNF-alpha mutein induces strong antitumor activity without overt toxicity--a review.

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Tumor necrosis factor (TNF-alpha) is a cytokine possessing antitumor and immunomodulatory properties. The studies reviewed in the present paper evaluate the effect of intratumor or intraperitoneal (i.t./i.p.) injections of human recombinant TNF-alpha (rhTNF-alpha) and its derivatives (muteins V and VI) on the course of experimental tumors. The aim of local cytokine administration was to avoid or reduce the induction of undesired systemic symptoms. Although total remissions were not observed in the studies, morphological analysis of lung tissue, accepted as the toxicity index of the cytokines, showed that rhTNF-alpha produced the least side effects. Mutein V selectively binds to p55R receptor and at the same time exhibits high antitumor activity. These results confirm the usefulness of studies on the structurally altered rhTNF-alpha derivatives, produced by means of genetic engineering techniques, which bind selectively to different cellular receptors of TNF-alpha and show similar or stronger antitumor activity compared with a native molecule, without inducing undesired symptoms.

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